NTP
National Toxicology Program

The National Toxicology Program Update

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NTP Board of Scientific Counselors
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Outline

- Staff changes
- Meetings of note
  - Report on Carcinogens expert panel meeting
  - Technical Report Review Subcommittee meeting
- Selected program initiatives/updates
  - NTP Laboratories
  - Biomolecular Screening Branch update
  - Public health context for NTP study results

Staff Changes

Welcome

- Dr. Kembra Howdeshell
- Dr. Andrew Rooney
- Ms. Kyla Taylor
- Dr. Jennifer Fostel
- Dr. Sue Fenton
- Dr. Jason Stanko
- Dr. Alex Merrick
- Dr. Mamta Behl
- Dr. Minerva Mercado-Feliciano
- Dr. Inok Surh
- Dr. Michael Boyle
- Dr. Torrie Crabbs
- Dr. Barry McIntyre
- Ms. Donna Roach

Active searches

- Pathology (1)
- Toxicology (1)
- Program Office (1)

Farewell

- Dr. Barbara Shane

Meetings

- Report on Carcinogens
  - Expert panel for formaldehyde – Nov. 2-4, 2009
- Technical Reports Review Subcommittee – Nov.-Dec. 2010 (estimate)
  - Acrylamide
  - Retinyl palmitate/retinoic acid phototoxicity studies
  - AIDS therapeutics studies
  - Kava kava extract
  - alpha-beta Thujone
  - Methyl trans-styryl ketone
  - Styrene acrylonitrile trimer
  - Pyrogallol

NTP Laboratories

- History
- Staffing
  - Fenton, Stanko, Dixon, Harry, Morgan, Sills
  - Others on as needed basis
- Focus
  - Immediate needs
  - Develop methods for developmental origins of adult disease
  - Worm toxicology
- Project development and review
- Facilities
  - Modules on E1

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Biomolecular Screening Branch Update

Ray Tice (Chief)

Bill Caspary

Alex Merrick*

Keith Shockley**

Tina Teng

Kristine Witt

Jon Freedman**

WormTox Screening Core

- Windy Boyd
- Paul Dunlap
- Julie Rice
- Daniel Snyder

** New staff*
***Position is adjunct to a primary appointment in Environmental Toxicology Program or Biostatistics*

The Tox21 Community Working Groups

- Pathways/Assays - K. Witt (NTP), K. Houck (EPA), M. Xia (NCGC)
  - Identify key toxicity pathways/assays (focus on cellular stress pathways in human cells) and prioritize assays
  - Identify methods for incorporating hepatic metabolism into in vitro assays
  - Consider approaches for evaluating compound, pathway, and cell-to-cell interactions
- Compounds - C. Smith (NTP), A. Richard (EPA), N. Southall (NCGC)
  - Establishing a library >10,000 compounds with known structures
    - Will include ~1/3 approved drugs, ~1/3 selected by EPA, ~1/3 selected by NTP, with some overlap among the 3 subsets
    - Purity, identity and stability assays underway
  - Establish a library of water-soluble compounds
  - Establish a library of mixtures

The Tox21 Community Working Groups (continued)

- Bioinformatics - K. Shockley (NTP), R. Judson (EPA), R. Huang (NCGC)
  - Evaluate patterns of response and relationship to adverse health outcomes in experimental animals and humans
  - Evaluate consistency of response within and across assays/endpoints
  - Make all data publicly accessible (CEBS, PubChem, ACToR)
- Targeted Testing - S. Masten (NTP), S. Edwards (EPA), J. Inglese (NCGC)
  - Prioritize substances for more complex testing, including the use of alternative assay platforms or species (e.g., C. elegans, zebrafish)

Phase I HTS assays used at the NIH Chemical Genomics Center (NCGC)

Cell Viability •ATP (13 cell types) •LDH •Protease release	**DNA Damage** •*p53* •Multiple repair deficient chicken DT40 cell lines	**Nuclear Receptors** •hAR •hERα •hFXR •hGR •hLXRβ •hPPARα •hPPARγ •hPPARδ •hPXR •rPXR •hRXR •hTRβ •hVDR
Apoptosis •Caspases 3/7, 8, & 9	**Epigenetics** •LDR	
Pathways •AP1 •ARE •CRE •HRE •NFκB	**Inter-individual Variation in Chemical Response** •Lymphoblastoid cell lines from 20 sets of identical twins	

Other Projects Underway/Proposed

- *C. elegans* Wormtox Group
  - Completed testing of ToxCast 320 in growth assay; analysis in progress
- Hemogenix
  - Effect of 25 compounds on *in vitro* CFC-GEMM, BFU-E, GM-CFC, TCFC and B-CFC from human, mouse, and rat bone marrow

17-beta-Estradiol	Cycloheximide
2',3'-Dideoxycytidine	Cyclophosphamide monohydrate
2-Aminoanthracene	Dichloroacetic acid
5-Fluorouracil	Ethinyl estradiol
Acrolein	Halothane
Azathioprine	Hydroquinone
Benomyl	Lead acetate (II) trihydrate
Benzene	Methoxychlor
Benzo(e)pyrene	Oxymethalone
Benzo[a]pyrene	Sodium tungstate dihydrate
Benzo(f)quinoline	Trichloroethylene
Bisphenol A	TCDD
Corticosterone	

- Conduct pilot toxicogenomic and proteomic studies on formalin-fixed tissue in NTP Archives
- Conduct deep sequencing pilot study on rat tissues and tumors

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Significant Advance

A Statistical Framework for Analyzing Quantitative High Throughput Screening Data (qHTS)

Shockley *et al.* have developed the capability to statistically analyze HTS data in an HTS mode. Tests first for concentration response, but if negative, also tests for whether average response across concentrations is different from control level.

SOT, 2010

NIEHS SBIR/STTR Contracts

- Development of Quantitative High Throughput Screens For Environmental Toxicants that Induce DNA Damage
- Development of Mid- to High-Throughput Toxicological Tests using Model Organisms
- Integrated Prediction Systems to Support Environmental Toxicological Assessments
- Incorporation of Metabolism into Quantitative High Throughput Screening Assays
- Development of Quantitative High Throughput Screens for the Detection of Chemicals that Modulate Gap Junction Intercellular Communication
- Monitoring *In Vivo* Gene Expression Changes after Exposure to Toxicants in *Caenorhabditis elegans*

* Proposals were due Nov. 9, 2009

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Tox21 Partnerships

Tice, R. Plenary Lecture, 6th World Congress on Animal Alternatives, Rome, Aug. 26-Sept. 3, 2009

"We now have the tools to advance toxicology from a largely observational science to one that is based on a comprehensive understanding of critical cellular pathways and how excessive perturbations to those pathways can result in disease.

Achieving this vision is an important goal of the NTP and NIEHS and one we are pleased to share with our colleagues at the NIH Chemical Genomics Center and the U.S. EPA. We invite others to collaborate with us and our partners in evaluating the utility of high throughput and high content screens for assessing the ability of chemicals to potentially induce adverse health effects in humans."

- FDA – Janet Woodcock (Director, CDER), Rose Cunningham (CDER). David Jacobson-Kram (CDER), Bill Slikker (Director, NCTR), Mitch Cheeseman (CFSAN)
- ATSDR – Bruce Fowler
- European Commission's Institute of Health and Consumer Protection – Maurice Whelen, Head, Systems Biology (HTS/HCS, Computational Toxicology, Metabolomics), Elke Anklam

EPA NCCT Board of Scientific Counselors

- BOSC meeting on Sept. 29-30, 2009
- Subcommittee: George Daston (Chair), James Clark, Richard DiGiulio, Ali Faqi, Lawrence Hunter, Moiz Mumtaz, Dennis Paustenbach, John Quackenbush, Santiago Schnell, Cynthia Stokes and Katrina Waters.

"*During the 4.5 years between its establishment and this review, the CTRP has made substantial progress in establishing and meeting priorities and goals; collaborating within and outside EPA to leverage the staff's expertise; and transforming the field of toxicity testing.*"

"*The BOSC strongly supports action by EPA to make the NCCT permanent.*"

Responsibility for Scientific and Public Health Context

- Problem
  - High content data, HTS, genomics, Toxicology in the 21st Century
  - New criteria for non-cancer endpoints
  - Societal expectations
- Solution
  - Internal discussions
  - Board of Scientific Counselors discussions
  - Executive Committee deliberations
- Expected outcome
  - Changes in organizational structure
  - Changes in programmatic expectations

Responsibility for Scientific and Public Health Context
(continued)

- Progress
  - New hires: Howdeshell, Rooney, Fostel
  - New processes, products, and scope for CERHR
  - CERHR input to FDA: soy formula and bisphenol A
  - Potential streamlining of Report on Carcinogens review process
  - New partners in Tox 21
  - Targeted testing
  - Herbals/Dietary supplement coordination with FDA
  - ICATM
- Outcome
  - Improved public understanding